DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781) 587-7500 Fax:(781) 587-7556 Industry Information: www.fda.gov/oc/industry	10/10/2012 - 11/09/2012* FEI NUMBER 3005881167

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Gregory A. Conigliaro, Vice President and General Manager

FIRM NAME	STREET ADDRESS
Ameridose, LLC	201 and 205 Flanders Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Westborough, MA 01581-1032	Sterile Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically,

Your firm manufactures admixtures from stock solution of active pharmaceutical ingredients or commercially available finished products. However, the firm does not test the potency of the final drug product after numerous lots are further diluted from these bulk stock solution. Moreover, your firm has received approximately 33 complaints claiming lack of effect, patient response events and ineffectiveness for products. For example: Ephedrine lot 02142012@372, Fentanyl lot 09042012@820, Oxytocin lot 12272011@1099 in 2011 and 2012. These lots were not tested for potency before release for commercial distribution.

This is a repeat item to the FDA 483 issued on 08/06/2008.

OBSERVATION 2

Each batch of drug product purporting to be sterile is not laboratory tested to determine conformance to such requirements.

Specifically,

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Your firm manufactures admixtures from stock solution of active pharmaceutical ingredients or commercially available finished products. These bulk stock solutions are tested commonly for sterility, and only the ones manufactured from active pharmaceutical ingredients are tested for the presence of bacterial endotoxin. The firm performs numerous manual aseptic manipulations in the filling of the sterile injectable drug products intended for patient use. Your firm does not test final units of finished product lots for sterility and the presence of bacterial endotoxin in finished sterile drug product lots after aseptic manual filling operations before release (e.g. Ropivacaine 0.2%, Lot 09262012@104.)

This is a repeat item to the FDA 483 issued on 08/06/2008.

OBSERVATION 3

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. Your firm failed to investigate microbiological contamination observed at least fifty three (53) times noted during (b) (4) sterility testing of sterile stock solutions intended to be used in the manufacture of sterile injectable drug products, including lots of Fentanyl, Ropivacaine, Morphine, etc. In approximately eighteen (18) instances your firm retested the affected stock solutions and microbiological contamination was also observed in at least one of the retest samples.

1. There is no documented evidence that suggests that a health hazard evaluation was initiated or conducted in order to assess the potential quality impact of microbiological isolates noted during the (b) (4) terility testing.

2. There is no data to support your firm's claim that all the sterility failures were attributed

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to contamination during the performance of the (b) (4) sterility method.

3. There is no documented evidence that your firm implemented permanent corrective actions to prevent these sterility events from recurring.

Furthermore, approximately (b) lots of sterile injectable drug products were manufactured and released from the affected stock solutions lots.

B. Your firm failed to adequately investigate three (3) sterility failures (OOS 12135 dated 04/26/2012 and OOS 12145 dated 05/03/2012). For example, the following was observed regarding two 2012 sterility failures (Sodium Bicarbonate stock solution lots S05022012@388 and S05022012@390 on 5/3/2012; and Hydromorphone 0.3 mg/mL stock solution lot S04242012 on 04/26/2012).

1. The investigation into the two sterility failures did not determine possible root causes of the contamination. Notably, it also lacked any meaningful corrective or preventive actions to prevent future non-sterility events.

2. The investigations failed to extend to all associated lots that may have been manufactured under the same inadequate practices or conditions that led to the microbial contamination of these lots.

3. Sterility test positive results were routinely considered questionable by the laboratory, and re-testing was done without justification. More specifically, when a positive result is obtained using the (b) (4) sterility testing method, your firm considers the initial positive to be an "inconclusive" or "suspect" result and performs re-testing. This is done although no laboratory cause of contamination has been identified. It is noteworthy that when further (b) (4) esting was done, the testing often revealed additional non-sterile units. This includes but not limited to all lots that are named in this observation.

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4. Your firm did not adequately differentiate or subculture microbes found in sterility test positives. Both lots that failed sterility were assumed to be cocci based on observation under microscope. However, despite multiple findings of contaminated units, no attempts were made to subculture the bacteria and further differentiate the microbe to determine its identity (e.g., gram stain, use of th(b) (4) available in your microbiology lab).

5. Insufficient relevant EM/personnel monitoring data was available from the production operations to correlate possible contamination sources in the environment with microbes found in sterility tests. Without knowledge of identity of microbes found during environmental monitoring, your firm lacked critical information to investigate possible root causes of the sterility failures.

C. The Quality Unit failed to adequately investigate, and implement permanent corrective actions after 45 environmental microbiological excursions (bacterial and mold) were isolated from critical areas such as personnel fingers inside class 100 hoods and controlled manufacturing areas (surfaces and air) during the manufacture of sterile injectable drug products in 2012. There is no documented evidence that suggests that a health hazard evaluation was initiated nor conducted in order to assess the potential quality impact of isolates present during the manufacture of sterile drug products. Furthermore, your firm does not perform identification of the observed microbiological isolates.

D. Your firm failed to adequately investigate complaints for the following reason(s):

1. Your firm's Quality unit failed to appropriately classify "patient response" complaints as adverse events. Additionally, your complaint investigations failed to address patient outcome or patient intervention.

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TYPE ESTABLISHMENT INSPECTED
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This includes the following complaints:

Complaint	Date Received	Drug Product	Lot	Description
AC11589	12/22/11	Oxytocin	12122011 @451	Communications between the firm and the complainant referenced "fetal distress and hyper stimulated uterus".
AC12430	9/6/12	Oxytocin	08252012 @73	Accompanying documentation states "customer called to report increased cases (5) of post partum hemorrhaging".
AC12118	2/15/12	Oxytocin	12162011 @131	Accompanying documentation states "patient had shortness of breath, the throat was closing, and coughing".
AC12070	1/24/12	Heparin	01062012 @336	Accompanying documentation submitted by the complainant states that the outcome of the adverse event to be "life-threatening".
AC12428	9/7/12	Fentanyl	09042012 @820	Accompanying documentation states "Patient was over sedated, unresponsive".

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AC12131	12/27/12	Fentanyl	01272012 @61	Communications between the firm and the complainant refer to 2 patients going into "respiratory distress" after receiving the medication.

2. Your firm's Quality unit failed to evaluate complaint sample(s) associated with the following complaints:

This includes the following Midazolam complaints which are associated with a "patient response" and low potency claims:

Complaint	Date Received	Midazolam Lot
AC12244	5/9/12	05012012@41
AC12186	3/26/12	02112012@245
AC12195	4/2/12	03282012@674
AC12120	2/23/12	12222011@157

This includes the following Oxytocin complaints which are associated with a "patient response":

Complaint	Date Received	Oxytoxin Lot
AC12030	01/11/12	12272011@1099
AC11589	12/22/11	12122011@451
AC12179	03/19/12	02162012@295, 02232012@260, 02242012@308
AC12409	08/27/12	08072012@301

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